AGING AND ATHEROSCLEROSIS

*Transcription of a Panel Meeting**

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MODERATOR SIMMS: This morning's panel discussion is on *Aging and Atherosclerosis,* which represent two extremely important medical problems.

First, I think it might be well to point out that, although this program is unrehearsed, we do have a list of questions so that the other members of the panel will know what to anticipate by way of subjects for discussion.

We have a few general questions. One of these asks for a definition of atherosclerosis. Literally the word means "soupy hardness" but that is hardly a definition of what we mean by atherosclerosis at the present time. Dr. Steele, would you care to venture a definition?

DR. J. MURRAY STEELE: I think to define atherosclerosis is a very difficult task. We are not certain that we are dealing with a single entity but I think Dr. Kendall has probably offered the best definition that there is when we are considering the particular disease that lays down the fatty plaque, the atheroma in the intima. I believe he likes to call it "intimal atherosclerosis" because of the notion that it really begins either in the intima or in the subintima and damage to the remaining part of the artery comes later.

MODERATOR SIMMS: *Dr. Kendall, would you care to comment further on that?*

DR. FORREST E. KENDALL: I was interested to hear that I had a definition! As a biochemist, I feel that I should leave this question of definition to those who have more background in clinical medicine and pathology.

DR. AARON KELLNER: One would think it would be possible at this time to give a fairly precise definition of what we mean by atherosclerosis. Unfortunately, as far as I am concerned, that is not the case. We must still define atherosclerosis essentially on morphological grounds, bearing in mind that what one individual calls atherosclerosis may not necessarily be atherosclerosis to another. My own prejudice as far as the definition is concerned is that atherosclerosis is a disease of the larger arteries which results in thickening of the intima and gradual narrowing of the lumen, and that one of the hallmarks, perhaps *the* hallmark, of the disease is the presence of lipid within the lesion, particularly in the early stages. There are differences of opinion about the role that the lipids play. It is my feeling that the lipids play an essential and fundamental role, that the infiltration of lipids is one of the basic phenomena of atherosclerosis. There are others, Duguid in England for

example, who feel that lipids are secondary, that thrombosis occurring on the intimal surface is the primary event, and the thrombus eventually organizes and produces the narrowing of the lumen. Winternitz in this country had a similar approach to atherosclerosis. He, too, felt that the lipid was secondary, that it resulted from the breakdown of blood clot following hemorrhage into the wall of the vessel. I think, however, that for purposes of this discussion, my colleagues on the panel would probably agree with me that we regard lipids as one of the essential features of the anatomical and perhaps also of the pathogenetic aspects of the disease. I have some photographs of atherosclerosis in human beings that I should like to show as illustrative material, either now or whenever you think it appropriate.

MODERATOR SIMMS: I would like to call on you a little later for that. In that connection it might be pointed out that, whereas atherosclerosis is an extremely important disease in man, it is not important in most animals. We have, as compared with other species, quite a long life span but the early death of most animals does not result from atherosclerosis. Chickens do have it. Cows, dogs, sheep, rats, rabbits don't normally have severe atherosclerosis.

The second question is in regard to the relationship between atherosclerosis and aging. Since this is a Fortnight on aging, it is appropriate that we comment on whether atherosclerosis is part of the aging process or whether, on the other hand, aging influences the incidence of atherosclerosis?

DR. STEELE: I think it has become increasingly clear that atherosclerosis is not necessarily part and parcel of the aging process. It is concomitant with aging. It is seen with increasing frequency with increasing age but one sees persons in the seventh and eighth decades, who die from other ailments, practically without atherosclerosis. Furthermore, atherosclerosis occurs in very young persons. The pathologists at McGill, Peck and others, showed at least one shower of fatty plaques in everyone over seven years of age. I believe that was the age they gave. Therefore it seems not to be directly connected with aging although as we live longer, as in many other diseases, we have a better chance to develop atherosclerosis.

MODERATOR SIMMS: Before going on to a discussion of the pathology, I would ask those in the audience who have questions to please write them out. They will be collected and we shall try to answer them to-

ward the end of the program.

With regard to the pathology of this condition I have two questions which I will ask of Dr. Kellner. The first question is to describe the early, as compared with the later, atherosclerotic lesions,—in other words, changes relative to the age of the lesion.

DR. KELLNER: The early lesions of atherosclerosis that we see with the naked eye or with the microscope result from the infiltrations of lipid material through the presumably intact endothelium into the intima of the blood vessel. There it is quickly taken up by phagocytes so that the first thing one sees is a tiny yellowish pin point or fleck on the vessel wall. Early in life one sees these in the aorta and very commonly on the aortic leaflet of the mitral valve. These small lipid aggregates at this stage are probably reversible. It is quite likely that before any other tissue changes ensue the lipid may disappear and leave little or no trace. However, in most human beings the process is a slowly progressive one, perhaps a cyclical one, and more and more lipid continues to be deposited in the vessel wall. As it does, the small lipid-rich plaques become larger and larger, protrude into the lumen and over a period of months and years, undergo secondary changes. These secondary changes are breakdown of the fat-containing cells with liberation of the fat, fibrosis, hyalinization and calcification. As the plaque gets larger and larger and as the lipid in the central portion of the plaque breaks down, blood vessels grow into the periphery of the plaque. Some of these vessels may rupture, producing hemorrhage into the plaque. As the plaque expands, the lumen becomes compromised; it becomes narrower and narrower and finally may be completely occluded. The lumen may become closed by the plaque itself or by thrombosis or hemorrhage superimposed on the plaque. Though we are all deeply interested in the phenomena that produce disability and death in atherosclerosis, namely, occlusion, thrombosis and hemorrhage into the plaque, I want to emphasize the point that, from a broad point of view, these are secondary phenomena. Important, to be sure, but nevertheless secondary. The underlying process, as I see it, is the infiltration of lipids into the vessel wall. Thrombosis and other disastrous accidents that occur are but the sequelae to this process.

(Slide) These few slides represent atherosclerosis as seen in a large metropolitan hospital. This is a very early atherosclerotic plaque just beneath the endothelium. This is intact endothelium, this the intima, and

here a small cluster of pale cells. These are histiocytes filled with lipid.

(Slide) This is a slightly later stage of the same process. Here is the normal endothelium; here you see a small hillock composed essentially of large pale cells which are filled with lipid material, and you see that at this stage it is already beginning to encroach ever so slightly upon the lumen. At this stage and in the preceding stage I think the process is probably reversible.

(Slide) This slide shows a much later stage in a coronary artery. At this point you see essentially normal artery wall, the intima and media of the coronary artery and here you see a large atherosclerotic plaque which has reduced the lumen of the coronary artery to less than half its original size. In the central portion of the atheromatous plaque there is much lipid and the surface here has become fibrosed and hyalinized.

(Slide) This is another coronary artery showing a far-advanced degree of atherosclerosis. Here is the normal thickness of the vessel wall and here you can see that about 80 per cent of the lumen of this vessel is filled with a large lipid-rich, atheromatous plaque. This pale area is lipid, much of which has been removed in the staining process necessary for preparing the slide. Here is the remaining narrowed lumen of the vessel—

(Slide) And this is an even more advanced stage. In this section several of the features of an older atherosclerotic plaque may be seen,—calcification, fibrosis, and hyalinization. This is a large grumous atheroma; if this is opened up, it is found to contain soft, almost cheesy material. The lumen of this coronary is enormously reduced in size, and this narrowing of the lumen is what results in the functional disability of the organ or tissue served by this vessel.

(Slide) This is the aorta of an aging individual showing a very extensive degree of atherosclerosis. Essentially the entire aorta is composed of coalescent atherosclerotic plaques. Dr. Simms asked the question,—how does one tell early lesions from late lesions? I think perhaps the easiest way is by the color. The earlier lesions are rich in lipid and therefore yellowish in color. In the later lesions, some of the lipid has disappeared and fibrosis and hyalinization have taken place, so that the later lesions have a grayish or pearly appearance. The lesions one sees commonly in the aortas of older people are the so-called pearly plaques, the plaques that have been present for months, years, perhaps decades.

There is one aspect of atherosclerosis of the aorta that I think is related to aging.

(Slide) This is a phenomenon we are seeing with increasing frequency, an atherosclerotic aneurysm of the aorta. This is related both to age and to atherosclerosis. Atherosclerosis occurs and plaques are laid down which in the aorta do not impinge upon the lumen particularly because the aorta is such a very wide vessel, but over a period of time there is a decrease in the amount of elastic tissue in the media. Gradually, due to the intrinsic pressure within the aorta, there develops an aneurysm, usually in the lower portion of the abdominal aorta. This appears to be related to aging. It is far more common in the sixth, seventh, and eighth decades and it is becoming increasingly common. It is due, I believe, to a combination of age and the effect of atherosclerosis upon the elasticity of the aorta.

MODERATOR SIMMS: *Dr. Kellner, would you care to comment on the fatty material that is deposited in the early versus later stages, namely, the proportion of sudanophilic stainable fat as compared with the cholesterol?*

DR. KELLNER: The studies on chemical composition of atherosclerotic plaques are really not very precise. They indicate in general that the earliest plaques contain lipid which is similar in composition to the lipid that is present in the plasma. Approximately a third of the lipid is cholesterol and its ester; another third is phospholipid; and the remainder neutral fat,—essentially what one finds in the plasma. As the plaques become older and undergo various secondary changes, one finds a higher proportion of cholesterol and cholesterol ester and a smaller proportion of phospholipid and neutral fat, probably because the phospholipids and neutral fat are more soluble and tend to disappear, whereas cholesterol stays behind. I think Dr. Kendall may have something to say about that.

MODERATOR SIMMS: *Dr. Kendall, do you wish to comment further on that?*

DR. KENDALL: No, I think that I agree essentially with Dr. Kellner's statement.

MODERATOR SIMMS: *The point I had in mind in asking the question is that, particularly in the very early plaques, we certainly don't have conspicuous cholesterol deposition. There is stainable material, essentially neutral fat, whereas the cholesterol becomes more conspicuous in*

the older plaques. The old idea that atherosclerosis consists merely of cholesterol deposition is, I believe, not correct. Would you agree with that, Dr. Kellner?

DR. KELLNER: Yes. The lipid that is deposited even in the very earliest lesions is not entirely cholesterol. However, that does not imply that cholesterol may not be important in the genesis of this lesion.

MODERATOR SIMMS: *I was not referring so much to the genesis as to the actual deposition. In that connection, I might ask Dr. Kendall,—in the feeding or injection of cholesterol, what is the nature of the fat that is deposited? That is certainly not all cholesterol.*

DR. KENDALL: No. When you feed cholesterol to the animal, a rabbit or a dog, or inject a colloidal suspension of cholesterol into the plasma, although the only thing administered is cholesterol, the lipid response found in the plasma includes changes in neutral fat and phospholipids as well as cholesterol. If you inject cholesterol without any phospholipid and neutral fat into a rabbit, you will find that 24 hours later the phospholipid in the plasma of the rabbit has increased in the same relative proportions that the cholesterol has increased and with this increase in cholesterol and phospholipid there is also an increase in neutral fat. I think that workers in the field have perhaps overemphasized the part played by cholesterol and it is becoming increasingly clear, I believe, that atherosclerosis should be considered a metabolic disease involving faulty or abnormal metabolism of all the lipids rather than of cholesterol alone.

MODERATOR SIMMS: *Let us go on to the next question. Dr. Kellner has commented on the changes, the differences with the age of the lesion. Would you now make some comments on the differences in the lesions relative to age of the patient?*

DR. KELLNER: I agree with the remarks made earlier by Dr. Steele, that while atherosclerosis is more common and seen more often as age progresses, it is not inherently due to the aging process. One sees atherosclerosis early in life. One sees clinically significant and often fatal atherosclerosis in the thirties and forties, and occasionally one sees people who come to postmortem examination at age 70, 80 or even 90 with remarkably little atherosclerosis. So that atherosclerosis is not, in and of itself, the result of the aging process, but rather a disease which is superimposed upon the aging process. It is a cumulative disease. Something happens to a blood vessel which results in tissue changes

that are not removed completely. The process is additive, and what we see at the time of death is the cumulative result of all the insults that have occurred to the blood vessels over a long period of time. So that, in general, with advancing age one finds more and more atherosclerosis in the aorta, in the coronary arteries, and in the cerebral arteries. If one takes any index of atherosclerosis, one sees a fairly good relationship between age and the amount of atherosclerosis. One finds, if one takes chemical indices, that the amount of calcium or the amount of cholesterol increases with age. This, then, is a phenomenon which is associated with age, although not inherently the result of the aging process.

DR. STEELE: May I ask Dr. Kellner a question? Dr. Lansing, who is speaking here tonight, has shown a progressive change from early adult life as to the deposition of calcium and some changes in the amino acids in the vessel wall. This bears no relation to the appearance of arteriosclerosis. It seems to be a very steadily progressive affair and the calcium is in fine, microscopic particles. Do you think that has any effect on the kind of lesion, the progress of the fatty plaque that you have been talking about?

DR. KELLNER: I think that is probably a separate phenomenon from the fatty plaques, Dr. Steele. I believe that in Dr. Lansing's study he carefully chose portions of vessels that had no atherosclerotic plaques. Changes such as he described are those that appeared to be associated with the aging process rather than with the disease that we are considering today.

MODERATOR SIMMS: *I think we can go on now to a discussion of some of the clinical aspects of atherosclerosis. Dr. Steele, would you please say a few words about the recognition of the presence of atherosclerosis?*

DR. STEELE: It strikes me that the recognition of the presence of atherosclerosis is one of the main stumbling blocks to our study of the disease clinically. Many persons may have extensive atherosclerosis, with many of their arteries involved, without exhibiting clinical signs. X-rays may show a good deal of calcium here and there, particularly in the aorta, as Dr. Epstein has recently shown. But for every one picked up by clinical study there must be many more who present the disease without recognition. The autopsy rate of atherosclerosis after the age of 50 would, I think, bear this out. One misses most of the atherosclerosis that occurs unless calcium is deposited or unless it happens

to land in a strategic spot, a strategic vessel, and gives rise to symptoms. As long as it leaves the lumen of the vessel open and simply confines itself to making the wall more rigid, there is almost no way of telling of its presence. But when it encroaches upon the lumen, particularly in such spots as the coronary and cerebral vessels or the vessels of the lower extremity, then serious clinical consequences that are readily recognized supervene. One must remember, however, that it is not always atherosclerosis that blocks a coronary or cerebral artery. It is by all odds, just the most common one.

MODERATOR SIMMS: *Would you care to say a few words about the clinical treatment of atherosclerosis?*

DR. STEELE: There isn't really any specific therapy for the underlying disease. I think one must divide the treatment of atherosclerosis into the treatment of the disease itself and treatment of the consequences of vascular accidents that result from atherosclerosis. When one talks about treating atherosclerosis I am afraid that, at the moment, to outline a treatment is fraught with difficulty. Dr. Kellner has already mentioned that in the very early stages the pathologic changes in experimental disease may be reversible. Also, the late Dr. Kenneth Turner showed that deposition of the fatty plaques can be partially prevented and their resorption enhanced by the use of thyroxin. This suggests that therapy is possible. The present state of knowledge of the pathogenesis of atherosclerosis is such that I don't believe one can outline a regime which, in a real sense, is either therapy or prevention of atherosclerosis. Obviously, it seems likely that diet plays a large role. Ancel Keys' studies and those of many others suggest very strongly that there is something in the diet that may increase the rate of development of these lesions but what it is, is not clear at the moment. Certainly it is not just cholesterol that is responsible. Other kinds of fats,—animal or vegetable, may be involved. Probably the best advice is just to avoid obesity. When one comes to the treatment of the accidents that happen along the road, then that treatment is the same as it would be had the accident come from a thrombus thrown from a rheumatic heart valve or other thrombo-embolic accident. If you have a patient with hemiplegia, I don't think it makes a great deal of difference whether he is old or young. You have simply to encourage him and try and get him to move the paralyzed extremity. It is always surprising to me what simple little things can help him along the way,—a rubber ball in the

paralyzed hand, to squash it, or to encourage him to read a newspaper aloud to recover his voice. If printed words are in front of him he learns much more rapidly to speak again. Many simple procedures, often called rehabilitation, can be carried out in the home as well as elsewhere. I don't think it is desirable to go into the whole regimen of treatment of coronary thrombosis because that subject is foreign to the major purpose of this panel today.

MODERATOR SIMMS: *What would you say is the effect of atherosclerosis on the clinical picture of the elderly patient, Dr. Steele?*

DR. STEELE: I think it is much the same as the effect on younger persons. There has been considerable difference of opinion about softening of the brain which may be part of atherosclerosis and the loss of memory for recent events which is also thought to be an atherosclerotic effect on the brain. I have never been sure of this relationship because many persons who have defective memories and who are not as mentally active and vigorous as others, apparently have little atherosclerosis. Again, the difficulty in recognizing its presence is the great stumbling block to real understanding of what part it plays, for example, in what are called senile psychoses. I don't believe a similar sized thrombosis causes any greatly different result in an elderly person than in a young person. There is, of course, one very interesting observation that Dr. Blumgart made many years ago,—that if a patient has had a prior occlusion of a coronary vessel (and as we grow older we can have several), then a subsequent occlusion may not produce cardiac infarction because of the collateral circulation which has developed following the previous occlusion. In the absence of that first small occlusion, with the production of collateral circulation, the second occlusion might have caused an infarct with serious results.

MODERATOR SIMMS: *There is one more clinical question which is perhaps another way of asking the same thing. Dr. Steele, how does the presence of atherosclerosis modify the medical treatment of the patient or how is it modified because of the presence of atherosclerosis?*

DR. STEELE: I am not sure that the presence of atherosclerosis would make one modify treatment in any way. Whenever one of the accidents due to atherosclerosis occurs that really causes disability then one modifies the treatment to suit the case whether it be coronary thrombosis, cerebral thrombosis or thrombosis in the artery to the leg which might result in gangrene. In other words, it is purely the treatment for

the result of atherosclerosis that alters the way you take care of the elderly, just as you would alter the way you take care of a similar accident in a much younger person.

MODERATOR SIMMS: *Dr. Kellner, would you care to add anything to Dr. Steele's comments on the clinical side of the problem?*

DR. KELLNER: I agree with Dr. Steele. I should like to make this comment, too, that atherosclerosis, certainly clinically significant atherosclerosis, is rare in animals. Nevertheless, if they are permitted to live out their normal life spans, there is deterioration of cardiac, renal, and cerebral function which occurs in aging animals even though they do not have atherosclerosis. It may well be that many of the things we rather glibly call atherosclerotic changes in the brain are not due to atherosclerosis but rather to some other phenomenon of aging.

MODERATOR SIMMS: We have been snowed under with questions so I think we had better start dealing with them. There are additional subjects on our agenda regarding the etiology of atherosclerosis and following that we will take up as many as possible of these questions from the audience. I don't think we will be able to cover them all by any means.

As to the etiology of this condition I am going to ask Dr. Kendall to comment on the current theories.

DR. KENDALL: There is almost universal acceptance today of the idea that some metabolic defect is the cause of atherosclerosis. There is no agreement whatsoever on what this metabolic defect is. It is believed by some that this metabolic defect is manifested by an increase in the beta-lipoprotein levels in human beings. I specify beta-lipoproteins rather than cholesterol levels because the bulk of the evidence today seems to indicate that the beta-lipoproteins play a special role in the development of the arterial lesions, a more specific role than does the serum cholesterol taken as an entity. For instance, the normal human being will have an average serum cholesterol level of about 200 mg. per cent. The average dog also has a serum cholesterol level of 200 mg. per cent but in the human being about 150 mg. of this 200 is present in the beta-lipoprotein fraction. In the dog only 40 to 50 mg. is present in the beta fraction. If by feeding cholesterol we increase the serum cholesterol level in a dog to 400 mg. per cent, a level which we might expect to produce atherosclerosis, we find there is no change in the ratio between the alpha and beta-lipoproteins. The cholesterol in the

beta fraction only reaches 80 to 100 mg. per cent, a value still much lower than the level of beta-lipoprotein normally found in most normal human beings. Under these conditions the dog does not develop atheromatous plaques. However, if we can maintain the serum cholesterol level of the dog at 400 to 500 mg. per cent and at the same time produce a change in the distribution of the cholesterol between the alpha and beta fractions, so that the dog now has 150 to 200 mg. per cent of cholesterol in the beta fraction, the dog will develop atheromata. Similar concentrations of beta-lipoprotein will produce arterial lesions in other experimental animals. For instance, normally a rabbit transports practically all of his cholesterol in the alpha fraction. But, if by feeding cholesterol or by any other means the level of the beta-lipoprotein is increased up to the level commonly seen in human beings, atheromata result. So it appears to be as though human beings have a metabolic pattern different from that found in animals, which results in the maintenance of the beta-lipoprotein at a point where atherosclerosis tends to develop. It may be that in clinical disease this abnormally high beta-lipoprotein level is superimposed upon other factors, which cause local damage to certain portions of the arterial tree. I am thinking particularly of the significant work done by Waters and de Suto-Nagy at Yale. They have shown that young dogs injected with certain pressor amines, including epinephrine, develop lesions in their coronary arteries and nowhere else. These lesions are not atheromatous. They would be described as arteritis. But if the concentration of beta-lipoprotein is increased, the lesions assume the appearance of typical atheroma.

I would say that to the best of my belief at present, atherosclerosis is a result of an elevated beta-lipoprotein level, perhaps combined with other localizing factors. I must point out that this elevated beta-lipoprotein level is not in itself a metabolic defect. It is the result of a process that is taking place elsewhere. The level of any component in the blood is determined not only by what is taking place in the blood but also by what is happening in the cells of the body. I believe the basic metabolic defect that leads to the elevated beta globulin is a defect that lies in the inability of the peripheral cells to take up and utilize the lipids which are supplied to them in the plasma. Whether we can pinpoint this defect in the future remains to be seen. There are certain bits of evidence at hand now that show that progress is being made.

One, it has been shown that the injection of heparin will increase

the individual's ability to clear lipid from the plasma. It has been shown that the clearing factor that appears in the blood is a lipase that splits the neutral fats of beta-lipoproteins. But this lipase originates in the cells. The effect of heparin is to liberate the lipase from the cells and permit it to get into the plasma and I am not at all certain that the appearance of this lipase in the plasma is an important factor. I think perhaps the presence of the lipase in the peripheral cells is the important thing. A cell has to have this lipase in order to begin the metabolic oxidation of fatty acids. Perhaps the heparin exerts its influence by modifying the surface of the cells. Heparin binds calcium. Calcium ions are necessary for the maintenance of the integrity of a cell wall. The appearance of the clearing factor in the circulating plasma may be the result of changes in the cell walls caused by the presence of an excessive amount of heparin that permits the lipase normally present within the cells to spill out into the blood. *This is speculation, which at present does not deserve to be given the name of a hypothesis, to say nothing of a theory.*

A far more significant observation, so far as the atherosclerosis is concerned, is the observation that patients with severe atherosclerosis produce less clearing factor in their blood following the injection of heparin. This may indicate that these individuals lack lipase in their peripheral cells.

All of us in this field are groping for some clue to the basic mechanism that results in the elevation of the beta-lipoprotein. Other clues are perhaps being furnished by the hormones. We know that various hormonal imbalances will produce marked changes in the serum lipid pattern, and I speak of hormonal imbalance rather than the effect of any specific hormone because I believe that it is impossible to introduce excessive amounts of any one hormone into a living animal without producing compensatory effects upon the complete hormonal balance that regulates metabolic processes in the body. One cannot affect the pituitary without affecting the thyroid and the adrenals and the pancreas. One cannot affect the gonads without producing compensatory effects in these other glands. So I think it is probably too early to discuss hormonal therapy in atherosclerosis intelligently. We do know that the only hormones which have been demonstrated to produce shifts in the alpha and beta-lipoprotein fractions are estrogens and androgens. Estrogens will tend to shift the cholesterol from the beta

to the alpha fraction. Androgens tend to produce shifts in the opposite direction. I think these shifts from one fraction to another are far more important than shifts in the level of serum cholesterol.

Much has been said in recent years about the effect of diet, about the possibility that high fat diets may play a part in the etiology of this condition. Much of the evidence that has been presented is rather convincing and I would be tempted to say that probably the high beta-lipoprotein concentration in human beings may be the result of an imbalanced hormonal picture upon an individual who is eating an unbalanced diet.

MODERATOR SIMMS: Dr. Kendall has given us a picture of the etiology of atherosclerosis but, as he pointed out in the beginning, there are many theories and many individuals working in the field who do not altogether agree with each other. So I think Dr. Kendall will agree that there are others who may not entirely subscribe to the picture which he has presented. My own work, for example, indicates that the important materials are not necessarily lipoproteins but other lipoid materials.

There are so many questions from the audience that I think we should turn our meeting over to an attempt to answer some of them. I regret that we will not be able to cover all of them.

First, there is a short but important question as to the relation of atherosclerosis to hypertension. Dr. Kellner, would you try to answer that?

DR. KELLNER: I think that atherosclerosis does not cause hypertension, and conversely, I do not believe that hypertension causes atherosclerosis. However, I do believe that hypertension has an important effect upon the development of atherosclerosis, an important accelerating effect. Lipids permeate the walls of blood vessels and the higher the inherent pressure in the vessel, the more lipid will permeate. In general, the higher the pressure, the more rapid and the more severe the development of atherosclerosis. I think this is true both in experimental animals and in human beings. Individuals with hypertension are more prone to develop clinically significant atherosclerosis of the coronary arteries and cerebral arteries. For example, females under the age of 40, who rarely get coronary artery sclerosis, do so if they have high blood pressure. If atherosclerosis results from the metabolic defect which Dr. Kendall has beautifully described, you might ask why does it not occur in veins?

Why does it not occur more commonly in the pulmonary artery? The same lipids are present in the veins as are present in the arteries. I think the answer, in part at least, is the pressure in these vessels. The vessels with the higher pressure are more apt to develop atherosclerosis. Veins which have little pressure have little or no atherosclerosis. The pulmonary artery which normally has a low pressure usually has little atherosclerosis. However, in those instances where the pulmonary artery pressure is elevated, as in mitral stenosis, one sees much more atherosclerosis. In the experimental animal, too, Dr. Kendall and his associates have shown that if one feeds dogs cholesterol and alters thyroid function by thiouracil, the animals develop hyperlipemia or hyperbetaglobulinemia and eventually develop atherosclerosis. If, in addition, the animals are made hypertensive and the lipid metabolic defect which has been shown to produce atherosclerosis in the dog is added, then the animals develop atherosclerosis very much more rapidly. To sum up, hypertension increases the speed with which atherosclerosis develops in experimental animals and probably also in human beings.

MODERATOR SIMMS: *Here is a question in regard to heparin admininstration: Is heparin administration of any value in the prevention of atherosclerosis? Dr. Steele, would you care to comment?*

DR. STEELE: I have just learned from Dr. Kendall a good deal about the action of heparin. Its administration might be useful if the betalipoproteins are so important in the development of the disease. Its administration is rather impracticable in long drawn out illnesses and one actually does not know that reducing the level of these lipoproteins would ameliorate arteriosclerosis.

MODERATE SIMMS: *Here is a question in regard to salt. What is the role of salt in the diet in atherosclerosis?*

DR. STEELE: I should not think it had any role. I don't know whether any definitive experiments have been done on the subject but certainly one must control the intake of salt when there is a disturbed electrolyte balance and the patient is accumulating fluid. Therefore in arteriosclerotic heart disease, with congestive failure one would probably want to restrict salt. Also some persons with arterial hypertension are able to stay on a very limited salt diet for long periods and can reduce the level of blood pressure somewhat. Insofar as hypertension is a factor in the development of atherosclerosis, reduction of pressure levels might aid in prevention.

MODERATOR SIMMS: *What would you say is the role of iodides in the treatment of atherosclerosis?*

DR. STEELE: I like that question! In the latter part of the last century when I was a youngster and my father was a practitioner of medicine, iodide was one of the really fine cure-alls for everything from 40 years of age on up. Iodides were given in courses of gradually increasing doses so as not to upset the stomach, in order to get the dose up as high as possible and then drop off again. It was supposedly useful in dissolution of the deposition of the fatty gumma of syphilis. It was similarly thought that one might dissolve the fat of the fatty plaques of arterial disease. A good many of my colleagues look askance at me when I give large doses of iodides today. It seems to be a favorite medicine of too long ago for anyone to use now. This is a purely clinical impression, but I do believe that some patients suffering from tinnitus and dizziness have been benefited by the use of iodides. Clinical improvement could be explained on the basis that a small early plaque in the pterygoid artery to the ear, which is enclosed in bone with no room to expand, had been dissolved or reduced in size. The evidence is very thin.

MODERATOR SIMMS: *Here is a question about an apparent disagreement between Dr. Kellner and myself in regard to the amount of cholesterol in the early plaques as compared with the later plaques. What I attempted to say was that in the early pin-point plaques, as far as the microscopic examination is concerned, the neutral, stainable fats predominate. One does not see cholesterol crystals, whereas the cholesterol crystals appear in the later plaques. Also, I might refer to Jobling and Meeker's work in which they found on chemical analysis that the proportion of cholesterol in the plaques is less in the early plaques than in the later ones.*

Now, Dr. Kellner, is there any disagreement between those comments and your opinion?

DR. KELLNER: I don't believe there is any disagreement at all, Dr. Simms.

MODERATOR SIMMS: *Does the ingestion of eggs influence atherosclerosis? Who wants to take that?*

DR. STEELE: For a great many years Dr. Steiner, who has worked with Dr. Kendall, has tried to alter the cholesterol level by feeding yolk of eggs to patients and Dr. Messenger and myself worked pretty hard at it too. It is surprising how many eggs you must eat before you

even begin to get an effect on the blood cholesterol level, after weeks and months of such feeding. Even then, although the levels ran a little bit higher, they were not much to brag about. However, Dr. Steiner did show that the cholesterol level often does run higher and is much more variable in persons with coronary disease. Although you probably would not want to try the experiment, if you feed very large amounts of eggs to people who have coronary atherosclerosis it might be that they will be less able to control their cholesterol level than normal people. Eggs also have a large amount of lecithin and where the cholesterol-lecithin ratio appears to be lower, as Pomerantz and Kunkel showed in a large group of diabetics, atherosclerosis is less likely to occur. If you manage to build up the blood phospholipids to a greater extent than the cholesterol, the eggs may well be good for you.

MODERATOR SIMMS: *Dr. Kendall, here is one for you. What significance do you attach to the lipoprotein spectrum of the blood in regard to the presence of atherosclerosis? I assume the person who asked this question is referring to Gofman's Sf* fractions, which Gofman claims do increase in atherosclerosis, particularly in the Sf20-400 fraction.*

DR. KENDALL: I find that a hard question to answer. I believe that the difficulty in answering questions of this kind arises from the fact that most adult Americans have some degree of arteriosclerosis. Just because an individual has not yet had a coronary attack, or has not developed a plaque in a position where it gives him symptoms is no reason for believing that the process leading to atheromata is lacking in this individual. I think that the Sf spectrum, lipoprotein spectrum of Gofman, will give you information about the relative height of the beta-lipoprotein level but I don't think it gives information that is much more valuable to the clinician than knowledge of the total serum cholesterol level. If the beta-lipoprotein is elevated to such an extent that it produces a significant change in the Gofman fraction it is going to be elevated enough to be significant in the serum cholesterol levels. Just as we do not know how to interpret the significance of a serum cholesterol value of 300 mg. per cent as compared with 250 mg. per cent, I am at a loss to compare an Sf12-20 level of 48 with one of 34. I think that the work on the ultracentrifuge is stimulating to this field but this work is still in the experimental investigational phase and we cannot apply it to individuals.

* Svedberg unit $=10^{-13}$ cm./sec./dyne/gm.

MODERATOR SIMMS: Dr. Kendall has touched on a serious research difficulty in atherosclerosis, namely finding or selecting individuals who have a propensity for atherosclerosis. If a patient has had a coronary attack we are dealing with someone who did have a propensity but we don't know that he has it at that time until after the attack particularly if he is under proper treatment. So we are handicapped in attempting to find a correlation between any measure of propensity toward atherosclerosis and the clinical picture in the patient.

I have a question which I will ask Dr. Kellner to discuss,—the difference between atherosclerosis and arteriosclerosis.

DR. KELLNER: Arteriosclerosis or hardening of the arteries is a general term, a term which includes within it more than one disease of blood vessels. Under the heading of arteriosclerosis we include, for example, atherosclerosis, the disease we have been discussing this morning. Another type of arteriosclerosis is the Mönckeberg type of sclerosis, which occurs usually in the lower extremities, which affects the media of blood vessels rather than the intima resulting in calcification, and which by itself does not narrow the lumen of the vessel. Another type of arteriosclerosis might be the change that occurs in very small blood vessels associated with hypertension. Yet a fourth type of arteriosclerosis might be the type of change that occurs with aging, where the elastic tissue of blood vessels undergoes degenerative changes and the vessels dilate and become tortuous, as can readily be seen in the corkscrew temporal arteries of most people in middle life. This is neither Mönckeberg sclerosis nor atherosclerosis, but a weakening of the elastic fibers of the vessel wall so that the wall undergoes dilatation, in both the longitudinal and transvere directions. Arteriosclerosis, then, is the generic term which refers to many different diseases of blood vessels. Atherosclerosis, we hope refers to a single specific entity among vascular diseases.

MODERATOR SIMMS: It is now time to close the meeting. If any of you wish to stay longer and discuss other questions personally, the panel members will be glad to do so. The meeting is adjourned.